## REMARKS

With this response, claims 29 and 30 have been cancelled. Claims 45-68 are newly added. Support for claims 45 through 52 can be found in the Specification at p. 16, lines 4-24; p. 59, line 6 through p. 60, line 21; p. 62, lines 4-21; p. 21, lines 14-29; p. 42, lines 21-27; p. 13, line 22 through p. 16, line 3; and Figure 3. Support for claims 53-56 can be found at p. 21, lines 14-29; p. 42, lines 21-27; and Figure 3. Support for claims 57-60, 67, and 68 can be found in the Specification at p. 30, lines 5-30; p. 35, lines 4-23; p. 75, lines 14-16; and p. 78, lines 16-21. Support for claims 61-66 can be found in the Specification at p. 34, line 27 through p. 35, line 1.

The Specification has been amended to correct the spelling of cysteine and remove an incorrect spelling of the same.

### I. 35 U.S.C. 112, First Paragraph – Written Description

Reconsideration is requested of the rejection of claims 29 and 30 under 35 U.S.C. 112, first paragraph as being unpatentable for lack of written description.

The Office rejected claims 29 and 30 as unpatentable because Applicants do not "describe all E1α, E1β, and E2 subunits of the branched chain oxoacid dehydrogenase complexes from all organisms other than *Arabidopsis*, or any other protein from any source that somehow 'enhances the biosynthesis of 2-oxobutyrate'," and therefore, given the breadth and lack of guidance, "the specification does not provide an adequate written description of the claimed invention." Applicants respectfully traverse. In support of the rejection under the written description requirement, the Office action cites *University of California v. Eli Lilly and Co.*, 119 F.3d 1559, 43 U.S.P.Q. 2d 1398 (Fed. Cir. 1997).

Rejected claims 29 and 30 have been cancelled; thus, the rejection as applied to these claims is moot. Newly added claim 45 claims a transformed plant, a plastid of which comprises polypeptides encoded by nucleic acid polymers encoding the E1α and E1β subunits and the E2 complex of the branched chain oxoacid dehydrogenase according to specific nucleotide sequences disclosed within the specification and a polypeptide encoded by a nucleotide sequence encoding an enzyme that enhances the biosynthesis of 2-oxobutyrate. Specifically, claim 45

claims a transformed plant, a plastid of which comprises polypeptides encoded by nucleic acid polymers encoding the E1α and E1β subunits and the E2 complex of the branched chain oxoacid dehydrogenase according to specific structures disclosed within the specification. The E1α, E1β, and E2 subunits of the branched chain oxoacid dehydrogenase complex are specified as proteins encoded by the nucleotide sequences SEQ ID NOs: 11, 13, and 15, respectively, or complements thereof; proteins encoded by nucleotide sequences that hybridize to those sequences based upon particular stringency conditions and maintain a requisite percent activity of the proteins encoded by the delineated sequences; proteins encoded by nucleotide sequences encoding the same amino acid sequences as SEQ ID NOs: 11, 13, and 15, but which are degenerate in accordance with the degeneracy of the genetic code and maintain a requisite percent activity of the proteins encoded by the delineated sequences; and proteins encoded by nucleotide sequences encoding the same amino acid sequences as the nucleotide sequences that hybridize to SEQ ID NOs: 11, 13, and 15 under particular stringency conditions, but which are degenerate in accordance with the degeneracy of the genetic code and maintain a requisite percent activity of the proteins encoded by the delineated sequences.

In contrast to *Eli Lilly*, Applicants are claiming a transformed plant, a plastid of which comprises polypeptides encoded by nucleic acid polymers described according to a specific sequence and encoding proteins that are described according to a specific sequence and function. Applicants are not claiming a broad genus without any structural limitations, but instead have claimed a plant comprising polypeptides encoded by nucleic acid polymers encoding proteins with specific structural characteristics predicated upon the disclosed nucleotide sequences SEQ ID NOs: 11, 13, and 15 and specific variations thereof, as disclosed immediately above. Additionally, structural characteristics of the proteins encoded by SEQ ID NOs: 11, 13, and 15 (*i.e.*, SEQ ID NOs: 12, 14, and 16, respectively) are described in the specification at p. 9, lines 22 through p. 11, line 11.

Furthermore, with respect to the enzymes that enhance the biosynthesis of 2-oxobutyrate, such enzymes are taught in the specification and are well known to those of skill in the art. As an example of the knowledge of one of skill in the art at the time of the filing of this application,

citation is made at p. 21, lines 14-29, and p. 42, lines 21-27 to Gruys, et al., WO 98/00557. Gruys teaches various enzymes, several ways in which 2-oxobutyrate can be provided in a plant, and common, well known methods of transforming plants with the same. Additionally, such enzymes are taught in Figure 3 of the specification. Applicants submit that such enzymes are used by those of skill in the art and the same are identified and described in the specification in sufficient detail such that "one skilled in the art can clearly conclude that 'the inventor invented the claimed invention.'"[1]

**II. 35 U.S.C. 112, First Paragraph – Enablement**

Reconsideration is requested of the rejection of claims 29 and 30 under 35 U.S.C. 112, first paragraph as being unpatentable for lack of enablement.

The Office rejected claims 29 and 30 as unpatentable under 35 U.S.C. 112, second paragraph, for lack of enablement, stating that Applicants do not teach plants transformed with any one of the many branched chain oxoacid dehydrogenase complexes from plants or microbes, any non-exemplified protein that somehow "enhances 2-oxobutyrate biosynthesis" or plant transformation with any combination of the various subunits of the complexes and any enhancement of 2-oxobutyrate biosynthesis therefrom. Applicants respectfully traverse.

As acknowledged by the Office, Example 7 teaches the combination of DNA sequences for branched chain oxoacid dehydrogenase complex E1α, E1β, and E2 complexes with the plastid targeting sequence of the pyruvate dehydrogenase complex E2 component to target the branched chain oxoacid dehydrogenase complex components to the plastid of a plant to form a hybrid complex with the plastid pyruvate dehydrogenase E3 component therein. Moreover, methods of production of transgenic plants are also taught in the specification.[2] Specifically, the utilization

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[1] *Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d. 1559, 1566, 43 U.S.P.Q.2d 1398, 1404 (Fed. Cir. 1997)(citations omitted).

[2] *See*, generally Specification, p. 25, line 27 through p. 49 line 26.

of plant promoters,[3] the construction of plant vectors,[4] plastid targeting,[5] and the transformation and regeneration of plants[6] are taught in the specification. Furthermore, these are also all skills that are well known in the art.[7] Such teachings in the application, in combination with the teachings of the Examples regarding the isolation, amplification, and combination of the branched chain oxoacid dehydrogenase complex components and enzymes that enhance 2-oxobutyrate synthesis, coupled with the information known in the art, are sufficient to enable one of ordinary skill in the art to make or use the claimed invention.[8]

Furthermore, an application need not contain a specific working example to be enabling.[9] Examples can simply be prophetic[10] or even non-existent all together. The absence of an example is not *per se* nonenabling, as the standard does not require examples, but merely a teaching that allows one of ordinary skill in the art to make or use the invention. In this particular instance, the teachings discussed above, in combination with the knowledge and skill

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[3] Specification at p. 27, line 1 through p. 28,line 20.

[4] Specification, p. 26, lines 6-29.

[5] Specification at p. 31, line 18 through p. 35, line 1.

[6] Specification, p. 28, line 21 through p. 30, line 30; p. 38, line 1 through p. 39, line 20.

[7] *See*, for example, Sambrook et al., Molecular Cloning, A Laboratory Manual, 3rd. ed., Cold Spring Harbor Laboratory Press, (2000) and Ausubel et al., Short Protocols in Molecular Biology, 4th. ed., John Wiley & Sons (1999).

[8] *U.S. v. Teletronics, Inc.* 857 F.2d 778, 785, 8 U.S.P.Q.2d 1217, 1223 (Fed. Cir. 1988) (The standard for enablement is that one of ordinary skill in the art be able to make or use the claimed invention from the disclosures in the application coupled with information known in the art without undue experimentation.).

[9] *Lawson v. Bruce*, 222 F.2d 273, 278, 105 U.S.P.Q. 440, 444 (C.C.P.A. 1955); MPEP § 608.01(p)[D].

[10] *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 750 F.2d 1569, 224 U.S.P.Q. 409 (Fed. Cir. 1984).

in the art, are sufficient to enable a person of ordinary skill in the art to transform a plant such that a plastid of the plant comprises the specific proteins and enzymes recited in the claims.

While the Office cites two references in support of its proposition that the state of the art of mixing subunits across species of multimeric enzymes is unpredictable, such articles are not applicable to the presently claimed invention in light of the amendments to the claims.

The Office cites Osterman et al. for the proposition that the formation of a cross species heterodimeric enzyme is highly unpredictable, as the formation of such did not occur between two cross species enzymes that shared only 40% identity. Specifically, Osterman et al. disclose the inability of an ornithine decarboxylase of the parasitic protozoa *L. donovani* to form a cross species heterodimeric enzyme with the ornithine decarboxylase from either of *T. brucei* or mouse, and that such is thought to be the result of the mere 40% sequence identity that *L. donovani* has with both *T. brucei* and mouse ornithine decarboxylase.

However, Osterman et al. additionally disclose that the formation of cross species heterodimeric enzymes does occur. Specifically, Osterman et al. disclose that the *T. brucei* and mouse ornithine decarboxylase are able to spontaneously form heterodimers. This occurs even though the two decarboxylase do not share exact sequence identity.

Furthermore, Osterman et al. do not properly address the manner in which the subject matter is currently claimed. Specifically, the claims, as amended, claim transformed plants with polypeptides encoded by specifically delineated nucleotide sequences, sequences that hybridize thereto and maintain a requisite percent activity, and degenerate sequences thereof that maintain a requisite percent activity. Osterman et al. do nothing to demonstrate that the use of homologous or degenerate nucleotide sequences as determined according to the claims is unpredictable or would result in unpredictably transformed plants. Therefore, Osterman et al. fail to demonstrate that the claims as currently amended encompass highly unpredictable embodiments. In the absence of such, the Office has failed to establish a *prima facie* case of nonenablement.

The Office also cites Larson et al. for the proposition that the ability to recover activity by an indiscriminate mixing of subunits of enzymes from across a broad range of species having the

same substrate preference is unpredictable due to changed amino acid residues that have been selected for maximizing specific interactions between subunits over evolutionary time. The Office asserts that Larson et al. disclose a site directed mutant of *C. reinhardtii* Rubisco P89R and wild type Rubisco activase from spinach and tobacco wherein a single amino acid substitution in the *C. reinhardtii* Rubisco large subunit resulted in a significant change in the activation preference from spinach Rubisco activase to tobacco Rubisco activase, as well as a significant loss in activity.

Specifically, sequences of Rubisco large subunits from three non-Solanaceae species and three Solanaceae species were compared, and single mutations within the large subunits were made. In determining the specific amino acid residue to change, Larson et al. excluded from consideration any residue that was identical with a sequence of one or more members of both groups. From the resulting list of twelve remaining residues, five more were eliminated because the replacements were "apparently conservative." Finally, residues that did not exist in the shorter non-Solanaceae large subunit were eliminated from examination. This left three sequences. Of the substitutions performed by Larson et al., the one indicated to have a detectable effect was that of proline to arginine. The result of this substitution was a significant loss in specificity (*i.e.*, activity).

Such a substitution is in stark contrast to the requirements of the currently amended claims. While the presently claimed invention encompasses transformed plants comprising polypeptides encoded by nucleotide sequences that are similar in sequence and thereby producing polypeptide sequences that are similar in sequence and function, Larson et al. were **specifically** in search of a substitution that could **completely alter enzyme activity**. Therefore, Larson et al. blatantly violate one of the elements of the claims as amended – specifically, the enzyme they produced does not have the requisite activity of the pre-modified enzyme.

Furthermore, Larson et al. do not properly address the manner in which the subject matter is currently claimed. Specifically, the claims, as amended, claim transformed plants with polypeptides encoded by specifically delineated nucleotide sequences, sequences that hybridize thereto and maintain a requisite percent activity, and degenerate sequences thereof that maintain

a requisite percent activity. Larson et al. do nothing to demonstrate that the use of homologous or degenerate nucleotide sequences as determined according to the claims is unpredictable or would result in unpredictably transformed plants. Furthermore, Larson et al. do not discuss hybridization or degeneracy of the nucleotide sequences encoding the proteins or the substitutions of the same studied therein. Therefore, Larson et al. inadequately demonstrate that the claims as currently amended involve a highly unpredictable art or encompass highly unpredictable embodiments. In the absence of such, the Office has failed to establish a *prima facie* case of nonenablement.

Furthermore, with respect to the enzymes that enhance the biosynthesis of 2-oxobutyrate, such enzymes and the nucleotide sequences encoding those enzymes are well known to those of skill in the art. As an example of the knowledge of one of skill in the art at the time of the filing of this application, citation is made at p. 21, lines 14-29, and p. 42, lines 21-27 to Gruys, et al., WO 98/00557. Gruys teaches various enzymes, several ways in which 2-oxobutyrate can be provided in a plant, and common, well known methods of transforming plants with the same. Additionally, such enzymes are taught in Figure 3 of the specification. Moreover, it is noted that a patent need not teach and preferably omits, what is well known in the art.[11] Applicants submit that such enzymes are used by those of skill in the art and the same are defined and identified in the specification such that a person of ordinary skill in the art could make or use the claimed invention from the disclosures in the application coupled with information known in the art without undue experimentation.[12]

**III. 35 U.S.C. 112, Second Paragraph – Indefiniteness**

The Office rejected claims 29 and 30 as unpatentable under 35 U.S.C. 112, second paragraph, for indefiniteness.

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[11] *In re Buchner*, 929 F.2d 660, 661, 18 U.S.P.Q. 2d 1331, 1332 (Fed. Cir. 1991).

[12] *U.S. v. Teletronics, Inc.*, 857 F.2d 778, 785, 8 U.S.P.Q. 2d 1217, 1223 (Fed. Cir. 1988).

The Office states that the phrase "a plant" is indefinite, as it fails to state whether the phrase refers to a transformed or untransformed plant or of a plant of any particular species. Applicants have canceled claims 29 and 30. Furthermore, independent claim 45 has been amended to specifically state "a transformed plant" thereby obviating the rejection.

The Office further states that the phrase "enhances" is indefinite, as it is unclear whether the phrase is meant to indicate an increase in the amount of product, more or less regulation of production of the product, or to include some novel biochemical improvement to the product itself. As described in the specification, "enhances" modifies "biosynthesis". The ordinary dictionary meaning of "enhance" is to make greater, to increase, or to augment. Additionally, a list of various enzymes that enhance biosynthesis of 2-oxobutyrate are listed at p. 21, lines 14-29. Furthermore, it is clear from the disclosed examples of such enzymes that the end result of their action is the increased or augmented production of 2-oxobutyrate. Therefore, the term "enhances" is definite, and would be understood by one of skill in the art as used in the claims of the present application.

## CONCLUSION

In light of the above arguments, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. 112, first paragraph, for lack of written description, under 35 U.S.C. 112, first paragraph, for lack of enablement, and under 35 U.S.C. 112, second paragraph, for indefiniteness.

Applicants request an extension of time to and including February 28, 2003, for filing a response to the above-mentioned Office action. A check in the amount of the applicable extension fee is enclosed. The Commissioner is hereby authorized to charge any deficiency or overpayment in connection with this amendment to Deposit Account No. 19-1345.

Respectfully submitted,

Timothy B. McBride, Reg. No. 47,781
SENNIGER, POWERS, LEAVITT & ROEDEL
One Metropolitan Square, 16th Floor
St. Louis, Missouri 63102
(314) 231-5400

TBM/sxm
Express Mail No. EV 224287122 US

## VERSION WITH MARKINGS TO SHOW CHANGES MADE

**IN THE SPECIFICATION:**

The paragraph beginning at line 1 of page 61 has been amended as follows:

Biologically functional equivalent nucleotide sequences of the present invention also include nucleotide sequences that encode conservative amino acid changes within the amino acid sequences of the present polypeptides, producing silent changes therein. Such nucleotide sequences thus contain corresponding base substitutions based upon the genetic code compared to the nucleotide sequences encoding the present polypeptides. Substitutes for an amino acid within the fundamental polypeptide amino acid sequences discussed herein can be selected from other members of the class to which the naturally occurring amino acid belongs. Amino acids can be divided into the following four groups: (1) acidic amino acids; (2) basic amino acids; (3) neutral polar amino acids; and (4) neutral non-polar amino acids. Representative amino acids within these various groups include, but are not limited to: (1) acidic (negatively charged) amino acids such as aspartic acid and glutamic acid; (2) basic (positively charged) amino acids such as arginine, histidine, and lysine; (3) neutral polar amino acids such as glycine, serine, threonine, cysteine, **[cystine,]** tyrosine, asparagine, and glutamine; and (4) neutral nonpolar (hydrophobic) amino acids such as alanine, leucine, isoleucine, valine, proline, phenylalanine, tryptophan, and methionine.

**IN THE CLAIMS:**

Claims 29 and 30 have been cancelled.

New claims 45-68 have been added.